REMARKS

No amendments are made to the claims.

Double Patenting

Applicants apologize for overlooking this matter in the last response. Enclosed herewith is a terminal disclaimer to satisfy this requirement.

35 USC § 103

Before discussing the issues of the application, Applicants point out that the affidavit that was filed under CFR § 1.132 with the last response was signed by an employee of the assignee of the present application, Allergan, Inc.

The Office Action alleges that the claims are obvious over Yamamoto ('906) and Nagpal ('279) in combination.

The Office disputes all of the Applicant's premises for asserting unexpected results except for one. These premises are listed below.

1) A general reduction of adverse events for the combination of tazarotene and a corticosteroid as compared to tazarotene alone is unexpected.
2) A general trend toward reduction in adverse events as corticosteroid potency is increased is unexpected.
3) Combining a corticosteroid with tazarotene is associated with a general reduction of adverse events as compared to tazarotene alone.
4) There is a general trend toward reduction in adverse events as corticosteroid potency is increased.

Points 1-2 deal solely with what is known or believed in the art. Points 3-4 deal solely with whether the results presented in the specification and the Gollnick references support Applicants interpretation of the data. The Office Action does not appear to dispute point 2.

1. A general reduction of adverse event for the combination of tazarotene and a corticosteroid as compared to tazarotene alone is unexpected.

As a general principle, when a treatment with a therapeutically active agent is unchanged except that an additional therapeutically active agent is administered, an increase in side effects is expected. This assertion is supported by the affidavit, which, quoting directly says, "[i]t is generally expected that administering two drugs to a patient will increase the adverse effects as compared to administering either of the individual drugs to the patient, where the dose of the individual drug is the same for individual and combination therapy." This is not attorney argument, but the testimony of an expert. The Office Action contradicted the expert and asserted "[t]he general expectation with combination therapy is a reduction in adverse effect." The Office claims that "[t]he adverse effect of the active ingredients might be different," and thus a person of ordinary skill in the art "would not expect" an increase in adverse events for a combination.

Applicants agree that active agents might have different side effects. However, this does not mean that a combination of those two active agents would not be expected to have an increase in adverse events. If active agent A has adverse effects M and N, and active agent B has adverse effects Y and Z, one would expect that combining them without changing the dose of either A or B would result in adverse effects M, N, Y, and Z. Thus, the combination has more adverse events (4) than the individual active agents (2 each). Because the adverse event contribution of each of the drugs in a combination may be different, the total number of adverse events is the most important quantity to be evaluated in terms of unexpected results. The Office has provided no evidence that a person skilled in the art at the time the application was filed would have believed that the present combination would not have more adverse events than the individual components alone. By contrast, Applicant has provided expert testimony that the general rule in the art is that combining drugs ordinarily increases the adverse effects. Therefore, the evidence of record supports Applicant's assertion.

2. A general trend toward reduction in adverse events as corticosteroid potency is increased is unexpected.

This assertion is supported by affidavit, which says "[i]t is generally expected that increasing the potency of a corticosteroid will increase the adverse events." Since this is not challenged by the Office Action, Applicants assume that this statement is accepted as true.

3. Combining a corticosteroid with tazarotene is associated with a general reduction of adverse events as compared to tazarotene alone.

This assertion is also supported by the affidavit, which states "there appears to be a general trend that combinations of tazarotene and corticosteroids increase efficacy in the treatment of psoriasis while reducing the adverse events as compared to tazarotene alone." Again, the Office Action rejects the testimony of an expert, not attorney argument. For support, the Office Action alleges "the data shows no difference with the utilization of med- versus high-potency corticosteroid and, thus, *does not support applicant's assertion of a trend towards a decrease in adverse effect with increase in the potency of corticosteroid.*" Even if it were true that there was no trend toward decrease in adverse effect with increase in the potency of corticosteroid, that conclusion does not prove that the combination does not have fewer adverse events than tazarotene alone. If anything, it actually supports the conclusion that combinations of tazarotene and corticosteroids increase efficacy while reducing adverse events for the present case.

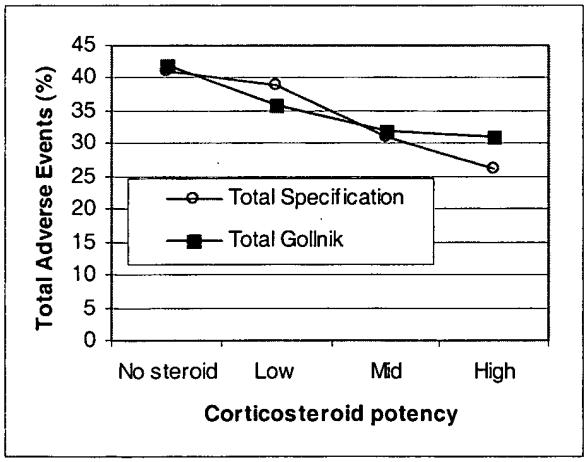
If there is no trend toward a decrease in adverse events with increasing corticosteroid potency, then all of the corticosteroids have essentially the same effect regardless of potency. If all of the corticosteroids have the same effect regardless of potency, then all of the corticosteroids can be treated the same when comparing them to tazarotene alone to determine whether the combination has reduced adverse events. Averaging the adverse event profile of the corticosteroid combination groups yields the data shown below. The table shows that corticosteroids significantly reduce the erythema significantly, and the pruritus and irritation somewhat. More importantly, as explained above, the total number of adverse events is the most relevant to unexpected reduction of

side effects, and the table shows an undeniable reduction in the total number of adverse events for the combination treatment. Thus, if one accepts that there is no trend in reduction of adverse events with increasing corticosteroid potency, one is compelled to conclude that the combination reduces the total number of adverse events as compared to tazarotene alone.

	Pruritus	Erythema	Irritation	Burning	**Total**
No steroid	15	12	8	6	**41**
Steroid	14	6	6	5	**32**

4. There is a general trend toward reduction in adverse events as corticosteroid potency is increased.

	Total Adverse Events (%) Specification	Total Adverse Events (%) Gollnik
No steroid	41	42
Low	39	36
Mid	31	32
High	26	31



Once again, this statement is supported by the affidavit, which states "there appears to be a trend of reduction in adverse events for the combination treatment of tazarotene and corticosteroid as the potency of the corticosteroid is increased." Gollnick

also states "there was a trend towards a lower incidence of treatment-related adverse events as corticosteroid potency increased." (p. 18, abstract, fifth line from bottom) As mentioned above, the Office Action disputes this expert testimony, claiming that the data shows "no difference" between the adverse events of the mid- versus high potency corticosteroid. This is not correct. Although the difference between the mid- and high potency is not as great as some of the other comparisons, there is still a difference, particularly when viewed with the other data. The table and plot above show both the data from the specification and the Gollnick reference. The trend is virtually impossible to miss. It is not correct to draw a sweeping conclusion from the one pair of points which shows the least difference while ignoring the overwhelming weight of the data. As mentioned before, the total adverse events is the most important comparison for unexpected results in the present case, and the data clearly supports a trend of decreasing total adverse events with increasing corticosteroid potency.

The Office Action also claims that the data "shows increase in burning in the taz/high group versus the other groups including the taz/plac group. It also shows an increase or no change in irritation in the taz/low versus the taz/plac group, similar incidence of erythema in all three groups given the corticosteroid; and an increase incidence of pruritus in taz/low group versus taz/plac group and an increase or no change in the taz/med group versus taz/plac." Applicants point out that data can indicate a trend while still having scatter and/or outlying data that does not fit with the general trend.

If one is to analyze any individual data points, all of the individual data points should be analyzed and compared to the proposed trend. The individual data is reproduced in the table below.

	Pruritus	Erythema	Irritation	Burning	**Total**
No steroid	15	12	8	6	**41**
Low	19	7	9	4	**39**
Mid	16	6	5	4	**31**
High	8	6	4	8	**26**

For each adverse event, there are six equally important comparisons which are relevant to the trend. These are comparison of no steroid to low, mid, and high potency (3); comparison of low potency to mid and high potency (2); and comparison of medium to high potency (1). Thus, there are 24 comparisons for the individual adverse events.

The table below shows whether each comparison is consistent with the trend, with a (+) indicating a consistent result and a (-) indicating an inconsistent result. No difference between two data points was considered to be a (-), and any difference consistent with the trend was considered to be a (+), even if it were only a difference of 1. The table clearly shows that with the exception of burning, comparing individual data points clearly favors a trend. A clear trend for three out of four of the individual adverse events indicates an overall trend. Approached another way, 16 out of the 24 data comparisons are consistent with the trend.

	Pruritus	Erythema	Irritation	Burning
No-low	-	+	-	+
No-mid	-	+	+	+
No-high	+	+	+	-
Low-mid	+	+	+	-
Low-high	+	+	+	-
Mid-high	+	-	+	-
Total +	4	5	5	2
Total -	2	1	1	4

One might say that a difference of 1% does not indicate a trend. However, if this is true, then a difference of -1% also is not inconsistent with a trend. The table below considers a difference of 1%, 0%, or -1% as being data which neither consistent nor inconsistent with a trend, and labels those differences as 0. In this case, the comparison of (+) to (-) is even more favorable, with the individual results for pruritus, erythema, and irritation even more strongly favoring a trend, and with the difference for burning being smaller. Furthermore, out of the data giving a (+) or (-), 13 out of 17 comparisons are consistent with a trend, which is a greater proportion consistent the trend than in the previous analysis.

	Pruritus	Erythema	Irritation	Burning
No-low	-	+	0	+
No-mid	0	+	+	+
No-high	+	+	+	-
Low-mid	+	0	+	0
Low-high	+	0	+	-
Mid-high	+	0	0	-
Total +	4	3	4	2
Total -	1	0	0	3

In conclusion, the expert testimony, the total number of adverse events, and a rigorous analysis of the individual data points for the individual side effects all support a trend for decreasing adverse events with increasing corticosteroid potency. There is really no analysis which fairly considers all of the data that supports a conclusion that the trend does not exist. Therefore, the Office Action has challenged expert testimony but has not supported the challenge.

Concentration of the Corticosteroid

In this and the previous Office Actions, Examiner continues to assert that the appropriate comparison is the concentration of the corticosteroid compound in the composition, and not the potency.

> ...the comparison is with different doses of corticosteroids. Based upon the utilization of the low, of low, med-, and high-potency, the skilled artisan would have the reasonable expectation that the effective amount of each group would decrease accordingly and thus, comparison would be based on decreasing doses of corticosteroid with increase potency. However, it is noted that the amount of high potency corticosteroid is twice the amount of med-potency corticosteroid in the present specification or for times the amount of low-potency corticosteroid in Gollnick reference.

As Applicant pointed out in previous responses, the appropriate comparison made by those skilled in the art is the potency of a corticosteroid formulation, not the concentration of the corticosteroid compounds. In the DECISION ON APPEAL of parent case Application No. 09/367,712, the Board sanctioned this position. For a fuller explanation, Applicant refers to that document, pp. 6-8.

In conclusion, as explained above Applicant believes that the claims are patentable as they now stand, and respectfully requests that Examiner pass them to issue.

Please use Deposit Account 01-0885 for any fees associated with this Amendment.

Respectfully submitted,

Brent A. Johnson

Date: 6-10-05

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CERTIFICATE OF FIRST CLASS MAIL UNDER 37 C.F.R. §1.10

I hereby certify that this Preliminary Amendment and the documents referred to as enclosed herein are being deposited with the United States Postal Service on **June 10, 2005** in an envelope as "First Class Mail Post Office To Addressee" with sufficient postage for First Class Mail addressed to Mail Stop: Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Bonnie Ferguson
Name of person mailing paper

Bonnie Ferguson
Signature of person mailing paper

Date: June 10 2005

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JOHN SEFTON

Appeal No. 2005-0938
Application No. 09/367,712

ON BRIEF

Before WILLIAM F. SMITH, ADAMS, and POTEATE, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-3, 5-8 and 10-13, which are all the claims pending in the application.

Claim 1 is illustrative of the subject matter on appeal and is reproduced below:

1. A method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a high-potency corticosteroid.

The references relied upon by the examiner are:

Yamamoto	5,236,906	Aug. 17, 1993
Nagpal et al. (Nagpal)	5,650,279	Jul. 22, 1997

GROUND OF REJECTION

Claims 1-3, 5-8 and 10-13 stand rejected under 35 U.S.C. § 103 as being unpatentable over Yamamoto and Nagpal.

We reverse.

PROCEDURAL BACKGROUND

This is the second time this application is before us on appeal. On September 24, 2003, a Decision was entered in the first appeal (Appeal No. 2002-1369) affirming a rejection of claims 1-3, 5-8 and 10-13 under 35 U.S.C. § 103 as being unpatentable over Yamamoto and Nagpal. Having concluded that the claims were upatentable over Yamamoto and Nagpal, the panel did not reach the only other ground of rejection in Appeal No. 2002-1369 - a rejection of claim 2 under 35 U.S.C. § 103 as being unpatentable over Smith[1] or Sequeira[2] in combination with Nagpal.[3] For clarity, we reproduce representative claim 1, as it was presented in 2002-1369, below:

1. A method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a mid- or high-potency corticosteroid.

As set forth in the Decision, page 3, "the examiner found Yamamoto teaches that it is known in the art to use adrenocortical hormones which are

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[1] Smith 5,874,074 Feb. 23, 1999

[2] Sequeira et al. (Sequeira) 4,775,529 Oct. 4, 1988

[3] A rejection of claim 2 under 35 U.S.C. § 103 as being unpatentable over Smith or Sequeira in combination with Nagpal was not presented to us on this appeal. Accordingly, we interpret this to mean that the examiner has withdrawn the rejection. Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys., 804 F.2d 659, 663, 231 USPQ 649, 651-652 (Fed. Cir. 1986), cert. denied, 480 U.S. 933 (1987).

among those utilized by appellant for treatment of skin diseases including psoriasis." In addition, the prior Merits Panel noted (id.), "[t]he examiner further found that Nagpal discloses that it is known to use tazarotene for treatment of psoriosis." According to the Decision (id.), the "examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art to have used the combination of mid- or high-potency corticosteroid and tazarotene for the treatment of proliferative skin diseases as claimed in view of the combined teachings of Yamamoto and Nagpal." Based on this evidence, the prior Merits Panel found (Decision, page 4), "the examiner has provided proper motivation for combining the [Yamamoto and Nagpal] references in accordance with the decision in Kerkhoven[4]." Accordingly, the rejection of claims 1-3, 5-8 and 10-13 under 35 U.S.C. § 103 as being unpatentable over Yamamoto and Nagpal, was affirmed.[5]

In affirming the rejection, the Merits Panel reviewed appellant's evidence of nonobviouness and made the following findings:

1. "Referring, first, to Example 1, the results of which are set forth in Figure 1, we note that the combination of tazarotene and a low-potency corticosteroid appear to provide better results than the combination of tazarotene and a mid-potency corticosteroid in reducing the severity of psoriasis in patients treated over a period of 12 weeks." Decision, page 5, emphasis added.

2. "[I]t is impossible to conclude from Table II[, appellant's specification, page 12,] that the incidence of adverse events was consistently lower

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[4] In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069 (CCPA 1980).

[5] We note, however, the prior Merit Panel's statement (Decision, page 7), "as the examiner failed to comment on appellant's evidence, we denominate our affirmance of the rejection as a new ground of rejection...."

in patients treated with mid- or high-potency corticosteroid in combination with tazarotene as compared with patients treated with low-potency corticosteroid in combination with tazarotene, or tazarotene alone. In particular, we note that patients suffered greater burning when treated with a combination of tazarotene and high-potency corticosteroid and a higher incidence of pruritus when treated with a combination of mid-potency corticosteroid and tazarotene." Decision, bridging paragraph, pages 5-6, emphasis added.

3. "Figure 2 shows treatment success in patients over a 12 week treatment period and four week post treatment period using the same four compositions. As with the results shown in Figure 1, it appears that the combination of low-potency corticosteroid and tazarotene provides better results than the combination of mid-potency corticosteroid and tazarotene." Decision, page 6, emphasis added.

4. "We do not find this Example [(Example 2)] persuasive in demonstrating unexpected results since the Example is unsupported by any data and is merely appellant's assertions that higher treatment success rates and decreased incidence of adverse events were provided when tazarotene was utilized in combination with mid- or high-potency corticosteroids." Decision, bridging paragraph, pages 6-7, emphasis added.

In response to the Decision, appellant elected to amend the claims and continue prosecution before the examiner. Specifically, appellant removed all references to "mid-potency corticosteroid" in the claims. Accordingly, the only corticosteroid encompassed by the claims before us on appeal is a "high-potency corticosteroid."

Against this backdrop, we now consider the merits of the rejection before us on appeal.

DISCUSSION

According to the examiner (Answer, page 3), the basis for the "rejection is set forth in a Board Decision mailed on September 24, 2003." We emphasize, however, that the scope of the claimed invention now before us on appeal is

different than the scope of the claimed invention in the previous appeal. Accordingly, the prior Merits Panel's findings of fact Nos. 1 and 3, discussed above, are no longer relevant to the claims now on appeal. Specifically, these findings address appellant's evidence, presented in Example 1, Figure 1 and Figure 2, regarding a combination of tazarotene and a low-potency corticosteroid relative to the combination of tazarotene and a mid-potency corticosteroid. The claims now on appeal are limited to a high-potency corticosteroid. As the appellant's evidence demonstrates in Example 1, Figure 1 and Figure 2, a combination of tazarotene and a high potency corticosteroid was more efficacious than the other combinations tested. See also Brief, page 3.

Appellant does not argue the merits of the combination of Yamamoto with Nagpal. Instead, appellant asserts (Brief, page 3), "[a]pplicant believes the specification of the present application contains evidence of unexpected results which are sufficient to overcome the obviousness rejection for the scope of the claims as currently amended, notwithstanding any prima facie [sic] obviousness that [e]xaminer and the Board allege exists." We interpret this statement to mean that appellant has conceded that the examiner has met her burden of establishing a prima facie case of obviousness. Accordingly, we turn to appellant's evidence of unexpected results.

In this regard, appellant points out (Brief, bridging sentence, pages 3-4), "[a]ccording to the Board's observations [in Appeal No. 2002-1369], increasing the potency of the corticosteroid has no apparent advantage in combinations up to mid-potency corticosteroids, thus it is surprising that the combination of

tazarotene and a high-potency corticosteroid should have such a significant improvement over the other treatments." More specifically, appellant asserts (Brief, page 4), Figure 1

> shows a clinically significant reduction in plaque elevation for the tazarotene/high-potency corticosteroid combination compared to the other treatments. Thus, the combination of tazarotene and a high-potency corticosteroid represents a subset which has enhanced efficacy relative to the larger group represented by the combination of tazarotene and a corticosteroid, which enhanced efficacy would not be predicted based upon the properties of the remaining part of the larger group.

Stated differently, the evidence of record demonstrates an unexpected result for the combination of tazarotene and a high-potency corticosteroid. We agree.

The examiner, however, is unconvinced. As we understand the examiner's assertion (Answer, page 5), the evidence of record does not provide a "true side-by-side comparison" of the reagents because different concentrations of corticosteroids were used. More specifically, in the Final Office Action[6], the examiner points out (bridging paragraph, pages 2-3), "Example 1 and the Figures compare alternative topical application of 0.1% tazarotene gel and a placebo, 1% hydrocortisone acetate (low-potency corticosteroid), 0.05% alcometasone dipropionate (medium-potency corticosteroid) or 0.1% betamethasone valerate (high-potency corticosteroid)." According to the examiner (Final Office Action, page 3), "in order to argue unexpected and/or unobvious results, the amount of corticosteroid in each case has to be kept constant."

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[6] Mailed December 3, 2003.

However, as appellant points out (Brief, page 5), since the potencies of the corticosteroids differ, a "comparison of a concentration of one compound to a concentration of a different compound is not proper." Rather, as we understand appellant's argument (Brief, page 6), the use of different concentrations of each corticosteroid effectively "normalizes" the cortocosteroids relative to their potency. According to appellant (id.),

> The potency of the corticosteroid is assigned according to the particular formulation in which it is contained. Thus, the 1% hydrocortisone acetate formulation used in the patent specification is considered to be low-potency at a concentration of 1% in the vehicle it is administered. The same is true for 0.05% alcometasone dipropionate being a medium-potency corticosteroid and 0.1% betamethasone valerate being a high-potency corticosteroid.

According to appellant (id.), "[t]he whole point of assigning potency to a corticosteroid formulation is to indicate the activity of that formulation, and thus treatment for a particular condition is determined according to the assigned potencies of the various corticosteroid formulations." In support of this assertion appellant relies on Cornell[7]. The examiner, however, fails to address appellant's argument or the Cornell reference, maintaining instead (Answer, page 5),

> [t]he examiner sees no reason why applicant could not utilize similar amounts of corticosteroids in each case. In addition, the utilization of low-, mid- and high-potency would imply that at identical concentrations, the efficacy of corticosteroids would be as recited and, thus, the skilled artisan would expect the high-potency corticosteroid to be most effective when used at similar concentration as the others.

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[7] Cornell et al. (Cornell), "Correlation of the Vasoconstriction Assay and Clinical Activity in Psoriasis," Arch Dermatol, Vol. 121, pp. 63-67 (1985).

The examiner, however, appears to miss the point. As the examiner recognizes the concentration of high-potency corticosteroid used in the experiments was 10-fold less than the concentration of low-potency corticosteroid. As appellant points out (Brief, page 6), the

> [e]xaminer's position is inconsistent with itself in that [e]xaminer alleges "[t]he skilled artisan would have the reasonable expectation that the higher concentration of betamethasone valerate [(a high-potency corticosteroid)] would result in better improvement over treatment with lower concentrations of alcometasone dipropionate [a medium-potency corticosteroid)]" but fails to recognize that the same reasoning would lead a skilled artisan to expect that the lower concentrations of alcometasone dipropionate [(a medium-potency corticosteroid)] and betamethasone valerate [(a high-potency corticosteroid)] relative to hydrocortisone acetate [(a low-potency corticosteroid)] would result in the treatment by the former two compounds being less effective. If the former two treatments are expected to be less effective, then the significant improvement of betamethasone valerate [(a high-potency corticosteroid)] over hydrocortisone acetate [(a low-potency corticosteroid)] that was observed must be unexpected.

Accordingly, we are not persuaded by the examiner's unsupported assertion regarding appellant's evidence.

Further, regarding the evidence presented in Table II of the specification, page 12, appellant asserts (Brief, page 4), "[a]ccording to Table II, the adverse events associated with the tazarotene/high-potency corticosteroid combination is at least as low or lower, than the other combinations with the exception of burning. Furthermore, the trend in the total number of adverse events points to a significant advantage for the tazarotene/high-potency corticosteroid combination." In support of this assertion, appellant provides the following table

(id.), which illustrates the downward trend in the total number of adverse events with increasing potency of the corticosteroid.

	Patients (%)			
	Taz/plac	Taz/low	Taz/med	Taz/high
Total Adverse Events	41	39	31	26

In view of the data tabulated in appellants table of "Total Adverse Events", we agree that the total number of adverse events is lower with the combination of Tazarotene with a high-potency corticosteroid that with tazarotene alone or with a low-potency corticosteroid.

As set forth in In re Hedges, 783 F.2d 1038, 1039, 228 USPQ 685, 686 (Fed. Cir. 1986):

> If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed. In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984).

On reflection, having considered appellant's evidence and rebuttal arguments in the context of the claims now before us on appeal, we find that the evidence of record weighs in favor of non-obviousness. Accordingly, we reverse the rejection of claims 3, 5-8 and 10-13 under 35 U.S.C. § 103 as being unpatentable over Yamamoto and Nagpal.

OTHER ISSUES

We note that claim 11 appears to contain a typographical error with reference to the claim from which it depends. As it now reads, claim 11 depends from itself. Prior to any further action on the merits, we encourage the examiner and appellant to work together to resolve this issue.

REVERSED

William F. Smith
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

Linda R. Poteate
Administrative Patent Judge

) BOARD OF PATENT
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